REMARKS

Claims 16 to 31 are pending in the application.

Claim Rejections - 35 U.S.C. 112

Claims 24-29 stand rejected under 35 U.S.C. 112, 2nd paragraph, as being incomplete.

The examiner states that the claims lack the essential feature of the rhenium compound as well as a base in the third container.

In regard to the "base", it is not understood what the examiner is referring to. The third container contains a substance such a citrate or acetate etc. that increases the pH value (relative to the acids being used in container 1).

In regard to the rhenium compound, it is respectfully submitted that the specification has explained in detail that the beta ray emitter rhenium-188 used for labeling is produced by a so-called radionuclide generator (available form Oak Ridge National Laboratory, TN, USA, or Schering AG, Germany). Once purchased, such a generator produces practically in unlimited quantities over several months the desired rhenium-188. Such a generator is suitable in particular for therapy with high radionuclide doses and several applications to the same patient. In such a generator, Re-188 is eluated in the form of perrhenate (oxidation state VII of Re-188) by applying an 0.9 % saline solution. The thus obtained Re-188 generator eluate has preferably a radioactivity of 1,000 MBq to 60,000 MBq, preferably of 10,000 to 20,000 MBq. This is set forth in the specification on page 7, 1st paragraph.

Such Re-188 generators are the usual source for obtaining the substance so that Re-188 can be prepared freshly - this is important because Re-188 has only a half-life of about 17 h. Clinical preparation of the particles labeled with Re-188 for use in a patient is therefore based on the Re-188 eluate of such a generator and appropriate kits - such as the claimed one - for labelling the appropriate particles.

Attached please find two articles (Zhang et al., vol. 18, no. 5, 2003, pp 719ff; Jeong et al., vol. 18, no. 5, 2003, pp 707ff) that deal with Re-188 therapy and the production of effective particles/compounds; on the second page (right column) of each article the generator and its use is described. See also *Jia et al. (page 109)* cited by examiner hwere such a generator is disclosed.

Therefore, Re-188 is NOT an essential component of the kit and is not part of the kit to be sold, but Re-188 is added by the user of the kit at the time of preparing the labeled particles for use in therapy. The specification has never stated or suggested that Re-188 is an essential part of the **KIT**. The specification sets forth that the invention - aside form the method being claimed - is directed to a **pharmaceutical kit for performing the method** according to the invention and that this kit - used for producing rhenium-188 labeled microspheres - comprises the following components (see last paragraph of page 7):

a) a container with a quantity of water-soluble tin-II salt and a complexing agent stabilizing the tin-II salt, each in a powder form or as a solution,

b) a second container with microspheres of human serum albumin, as well as

c) a third container with a substance or solution for increasing the pH value, in powder form or as a solution.

The claim 24 as now worded is therefore complete as it is the kit (its parts) as such that is being claimed and not the Re-labelled compound that is to be produced by using the kit.

The claims 24 to 29 are further rejected under 35 USC 112 as being indefinite because the wording in regard to quantity for increasing the pH value contains too many variables. Claim 24 therefore has been amended to include specific values for the individual compounds.

Claim 28 is rejected because of "per administration to the patient". Examiner points out that the kit is not a method of treating so that this wording is indefinite. The claim has been amended to define that the specific quantities now set forth define a single dose that is to be administered.

Reconsideration and withdrawal of the rejection of the claims under 35 USC 112 are respectfully requested.

Rejection under 35 U.S.C. 102

Claims 24-25, 27, 29-31 stand rejected under 35 U.S.C. 102(b) as being anticipated by *Jia et al. (1995)*.

Examiner argues that *Jia et al.* discloses a vial with tin(II)chloride, citric acid and

gentisic acid and a second vial with 15 mg HSA spheres. A third container is supposedly disclosed that contains sodium citrate (page 108). The chemicals in three separate containers in examiner's opinion meet the limitations of the kit.

The particles of claims 30-31 are in examiner's opinion anticipated because the particles made in *Jia et al.* are prepared by the same method steps as claimed - including heating and re-suspending in isotonic saline at pH 7.4.

Amended claim 24 no defines that the pharmaceutical kit for producing particles labeled with Re-188 comprises:

a) a first container containing 0.02 mmol to 0.1 mmol water soluble tin-II salt and 0.5 mol to 2 mol complexing agent for stabilizing the tin-II salt, the complexing agent selected from 2, 5-dihydroxy benzoic acid, acetic acid, citric acid, malonic acid, gluconic acid, lactic acid, hydroxy isobutyric acid, ascorbic acid, tartaric acid, succinic acid, salts of said acids, or glucoheptonate, the tin-II salt and the complexing agent each present in solid form or in aqueous solution;

b) a second container with 1 to 20 mg particles made from an organic polymer or a biopolymer;

c) a third container containing 0.01 mmol to 0.2 mmol of a substance for increasing the pH value, the substance selected from citrate, acetate, or tartrate, present in solid form or in aqueous solution, wherein the substance, when added to a mixture of the contents of the first and second containers, generates in aqueous solution a pH value of pH 6.5 to pH 8.5.

Thus, claim 24 sets forth a kit of three containers, each containing a specific amount of a specific substance or substances. More specifically, the third container contains a substance that, when added to a mixture of the contents of the first and second containers, generates in aqueous solution a pH value of pH 6.5 to pH 8.5.

The examiner argues that sodium citrate is disclosed in *Jia et al.* and that therefore a third container with sodium citrate is disclosed as part of the kit of *Jia et al.* It is respectfully submitted that aside form being listed in the "Materials and methods" section of *Jia et al.*, there is no other mention of sodium citrate in the entire reference. Nowhere is there any disclosure as to how and where and for which purpose it is used. There is no

suggestion that it has anything to do with the preparation steps of the Re particles. Therefore, there is no suggestion that this substance could be part of the kit and there is no suggestion that when added to a mixture of the contents of the first and second containers, it generates in aqueous solution a pH value of pH 6.5 to pH 8.5.

Moreover, no quantities of the substances in any of the containers is disclosed in this reference (the section regarding direct labeling of microspheres with Re186 and Re188 is silent as to quantities (see middle of page 110).

Claim 24 is therefore not anticipated by *Jia et al.*

Claim 30 relates to the ready-to-use product prepared by the method as claimed in claim 16, where it has been specified that to the solution of step b) a buffer substance is added for increasing and adjusting the pH value of the solution to pH 6.5 to 8.5. This means that to the solution that has been heated, the pH-adjusting substance is added and the preparation is ready to use. No washing, centrifuging or re-suspending steps are required.

The yield (radiochemical purity) achieved by the invention is 95 % after a total time of 1 hour (55 minutes at 95 degrees C + 5 minutes incubation after pH increase as disclosed in example 1 of page 12 of the specification). The purity of 95 % is a major achievement; radiochemical purity over 95 % is generally needed for a radiopharmaceutical to be effectively used (see attached copy of Textbook of Radiopharmacy, page 109, left column, 2nd paragraph under the heading 9.3.1 Introduction). Because the method according to the invention achieves radiochemical purity over 95 % as evidenced by the examples, the microspheres labelled by the method according to the invention can be directly injected into the patient without carrying out any washing steps (see page 10, 1st paragraph of the specification; emphasis in bold added):

"*For producing Re-188 labeled microspheres, the tin-II salt and the complexing agent for stabilizing the tin-II salt are dissolved in the first container in sterile water and added to the second container containing the microspheres and the microspheres are suspended in the solution. The generator eluate containing the radioactive rhenium-188 is added to the suspension and the suspension is heated to 80 °C to 100°C. After 45 minutes to 70 minutes of heating, the pH value is adjusted to pH 5 to pH 8.5 by mixing the suspension with the* ***substance for increasing the pH value*** *that is contained in the third*

container. The ***suspension*** *is now cooled, preferably to body temperature, and* ***can be administered without washing steps directly to the patient****.*"

Thus, only the buffering substance (e. g. citrate or acetate or tartrate to adjust the pH-value) has to be added to the suspension of microspheres (radioactive) and the resulting suspension as is can be directly administered to the patient, leaving no radioactive waste. The invention is surprising in that the single simple step of changing the pH-value can increase the labelling efficiency to more than 95 % (after 1 hour) thus enabling direct use of the preparation (see also page 4, 2nd paragraph, of the specification).

The method according to *Jia et al.* requires a separation step (centrifugation) of the labeled microspheres followed by thorough washing with DI water or isotonic saline. In contrast to the present invention, in *Jia et al.* the Re labeled product contains no supernatant and no added buffer substance; the supernatant has been removed and replaced with DI water or saline solution. Washing or separation steps are disadvantageous because they lead to loss of radioactivity and expose the medical personnel to radioactivity.

Claim 30 is not anticipated by *Jia et al.*

Reconsideration and withdrawal of the rejection of the claims under 35 USC 102 are respectfully requested.

Rejection under 35 U.S.C. 103

Claims 24-31 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Jia et al. (1995) and Sailerova et al (2003)* and *Rhodes*.

The reference to *Jia et al.* has been discussed in detail supra and reference is being had to this discussion.

Sailerova is cited by examiner to show a specific amount of tin in the solution as well as tartrate as a buffer to make Re-labeled microspheres. *Rhodes* teaches sodium potassium tartrate.

It is respectfully submitted that *Sailerova* employs tartrate as a chelating agent for a transchelation from Re-tartrate to Re-HSA; see left column of page 312 (last full paragraph). The effects of pH, molarity, reductant level and temperature on the stability

and labeling yield of Re tartrate are studied. The Re tartare is produced from Re perrhenate in tartrate buffer by electrolysis on tin electrodes (see page 312, right column, 2.1 Tartrate labeling procedure) to produce the desired tin level in the solution. The HSA is then added to the electrolysis solution to observe the transchelation. Examiner contents that labeling at 800 microgram / ml complete labeling of the microspheres is reached. This is not so; the reference to complete labeling refers to the Re tartrate chelate (page 315, right column, lines 4-8; Fig. 2). The effects in regard to transchelation and the yield of transchelated albumin is illustrated for example in Figs. 6 and 7 (page 317). Generally, it is reported that the labeling yield varies greatly as a function of various factors (see left column of page 317), and albumin concentration itself appears to be the greatest factor.

Sailerova teaches that the electrolysis preparation is used in the subsequent step of transchelation, i.e., the albumin solution is added to the electrolysis solution and the reaction is carried out at room temperature at pH 4.5 (see page 313, 2.2 Albumin labeling). No subsequent step of increasing the pH value is described.

The reference does not teach a (tartrate) buffer that, when added to a mixture of the contents of the first and second containers (electrolysis preparation and albumin solution), generates in aqueous solution a pH value of pH 6.5 to pH 8.5.

This reference may teach a range for tin concentration in the electrolysis solution, but no specific values as claimed in instant claim 24 for the substances in all of the three containers of the kit.

As *Jia et al.* is also silent as regards values as claimed in claim 24 and the buffer substance, the claim 24 is not obvious in view of the cited reference combination as there is no teaching or suggestion how to arrive at the specific claimed values.

As regards claim 30, reference is being had to the above discussion (under 35 USC 102) of the method according to *Jia et al.* where a separation step (centrifugation) of the labeled microspheres followed by thorough washing with DI water or isotonic saline is required. In contrast to the present invention, in *Jia et al.* the Re labeled product contains no supernatant and no added buffer substance; the supernatant has been removed and replaced with DI water or saline solution.

Since *Jia et al.* does not disclose buffer substance being added and does not disclose a read-to-use preparation including the buffer substance, the combination of the

two references *Jia et al.* and *Sailerova* cannot make obvious claim 30 as *Sailerova* is entirely silent in regard to a further treatment step and buffering substance being added to the transchelation product.

Reconsideration and withdrawal of the rejection of the claims under 35 USC 103(a) are respectfully requested.

CONCLUSION

In view of the foregoing, it is submitted that this application is now in condition for allowance and such allowance is respectfully solicited.

Should the Examiner have any further objections or suggestions, the undersigned would appreciate a phone call or **e-mail** from the examiner to discuss appropriate amendments to place the application into condition for allowance.

Authorization is herewith given to charge any fees or any shortages in any fees required during prosecution of this application and not paid by other means to Patent and Trademark Office deposit account 50-1199.

Respectfully submitted on August 24, 2010,

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GEH
Encl:
- Zhang et al., vol. 18, no. 5, 2003, pp 719ff
- Jeong et al., vol. 18, no. 5, 2003, pp 707ff
- Textbook of Radiopharmacy, Charles B. Sampson Ed. (1994) page 109